1,2-Dichloroethane

Dutch Expert Committee on Occupational Safety (DECOS)
A committee of the Health Council of the Netherlands

To: the State Secretary of Social Affairs en Employment
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Health Council of the Netherlands

contents

samenvatting

Op verzoek van de minister van Sociale Zaken en Werkgelegenheid (SZW) heeft de Gezondheidsraad gezondheidskundige advieswaarden afgeleid voor de beroepsmatige blootstelling aan de kankerverwekkende stof 1,2-dichloorethaan. Dit advies is tot stand gekomen in de Commissie Gezondheid en beroepsmatige blootstelling aan stoffen (GBBS). Op www.gezondheidsraad.nl staat meer informatie over de taken van deze vaste commissie van de Gezondheidsraad. De samenstelling van de commissie is te vinden achterin dit advies.

Gebruik van 1,2-dichloorethaan

1,2-Dichloorethaan wordt voornamelijk gebruikt voor de productie van vinylchloride, het uitgangsmateriaal voor PVC (polyvinylchloride). De stof is geclassificeerd als ‘verondersteld kankerverwekkend voor mensen’ (gevarencategorie 1B). Op advies van haar Subcommissie Classificatie carcinogene stoffen, beschouwt de commissie de stof als stochastisch genotoxisch, dat wil zeggen dat de stof directe schade aan het genetisch materiaal (DNA) veroorzaakt.

Gezondheidskundige advieswaarden op basis van extra risico

Voor kankerverwekkende stoffen die geclassificeerd zijn in categorie 1A of 1B en die directe schade aan het genetisch materiaal veroorzaken (stochastisch genotoxisch werkingsmechanisme) kan geen blootstellingsniveau worden afgeleid waar onder ze niet kankerverwekkend zijn. Om voor deze stoffen toch een grenswaarde te kunnen bepalen, heeft de minister van SZW risiconiveaus vastgelegd. Deze risiconiveaus betreffen het extra risico op kanker door beroepsmatige blootstelling gedurende het arbeidzame leven. Het streefrisiconiveau is niet meer dan 4 extra gevallen van kanker op 100.000 sterfgevallen in de algemene populatie; het verbodsrisiconiveau is 4 op 1.000. De commissie schat de concentraties van een stof in de lucht die overeenkomen met die risiconiveaus, uitgaande van 40 jaar beroepsmatige blootstelling.

Geraadpleegde onderzoeken

Er zijn geen onderzoeken beschikbaar naar blootstelling aan 1,2-dichloorethaan en het optreden van kanker bij de mens die geschikt zijn voor het afleiden van gezondheidskundige advieswaarden. Er zijn verschillende dieronderzoeken gedaan naar het optreden van kanker door blootstelling aan 1,2-dichloorethaan. De commissie heeft deze onderzoeken beoordeeld en de meest geschikte geselecteerd. In dat onderzoek werden muizen langdurig blootgesteld aan 1,2-dichloorethaan in de lucht en kregen ze verschillende soorten tumoren. Het aantal kwaadaardige borsttumoren in vrouwtjesmuizen is door de commissie gebruikt voor het afleiden van de gezondheidskundige advieswaarden.

Advies aan de staatssecretaris

De commissie schat de concentratie van 1,2-dichloorethaan in de lucht die samenhangt met een extra risico op kanker van 4 per 100.000 (het streefrisiconiveau) gelijk aan 0,126 mg/m^3. Een extra risico op kanker van 4 per 1.000 (het verbodsrisiconiveau) komt overeen met een concentratie van 12,6 mg/m^3. Beide schattingen gaan uit van een beroepsmatige blootstelling gedurende 40 jaar.

Verder adviseert de commissie om een huid-notatie (H-aanduiding) toe te passen voor 1,2-dichloorethaan omdat deze stof relatief makkelijk kan worden opgenomen via de huid en zo substantieel kan bijdragen aan de totale inwendige blootstelling.

executive summary

At the request of the Ministry of Social Affairs and Employment, the Health Council of the Netherlands has derived health-based recommended values for 1,2-dichloroethane. This advisory report has been composed by the Dutch Expert Committee on Occupational Safety (DECOS). More information on the tasks of this permanent committee of the Health Council of the Netherlands can be found at www.healthcouncil.nl. The members of the Committee are listed at the end of this report.

Use of 1,2-dichloroethane

1,2-Dichloroethane is primarily being used in the production of vinyl chloride, the monomer unit of polyvinyl chloride (PVC). The substance is classified as a category 1B carcinogen (*presumed to have carcinogenic potential for humans*). As recommended by the Subcommittee on Classification Carcinogenic Substances, the Committee considers 1,2-dichloroethane as a stochastic genotoxic carcinogen.

Recommended values based on extra risk of cancer

For carcinogenic substances that have been classified in category 1A or 1B and directly interact with DNA (stochastic genotoxic mechanism), no exposure level can be derived below which no carcinogenic effects can occur. To be able to set occupational exposure limits for these substances, the Minister of Social Affairs and Employment has determined risk levels. These risk levels relate to the extra risk of cancer due to occupational exposure. The target risk level is 4 extra cancer cases per 100,000 deaths in the general population; the prohibitive risk level is 4 per 1,000. The Committee estimates the concentration of a substance in the air that corresponds to these risk levels, taking into account 40 years of occupational exposure.

Consulted research

There are no studies available on exposure to 1,2-dichloroethane and cancer in humans that are suitable for deriving health-based recommended values. Several animal carcinogenicity studies have been performed with 1,2-dichloroethane. The Committee has evaluated these studies and selected the most appropriate study. In this study, mice that were chronically exposed to 1,2-dichloroethane by inhalation developed different types of tumours. The number of malignant mammary tumours was used to derive health-based recommended values.

Recommendation to the State Secretary

The Committee estimates the concentration of 1,2-dichloroethane in the air that corresponds to an extra cancer risk of 4 per 100,000 (the target risk level) equal to 0.126 milligram (mg)/per cubic metre air (m^3). An extra risk of cancer of 4 per 1,000 (the prohibitive risk level) corresponds to a concentration of 12.6 mg/m^3. Both estimates are based on 40 years of occupational exposure.

In addition, the Committee recommends to apply a skin notation for 1,2-dichloroethane because the substance is absorbed by the skin relatively well, and can thereby contribute substantially to the total internal exposure.

01 scope

1.1 Background

In the Netherlands, occupational exposure limits for genotoxic chemical substances are set using a three-step procedure. In the first step, a scientific evaluation of the data on the toxicity of the substance is made by the Dutch Expert Committee on Occupational Safety (DECOS), a committee of the Health Council of the Netherlands, at request of the Minister of Social Affairs and Employment. This evaluation should lead to a health-based recommended exposure limit (HBROEL) for the concentration of the substance in air. Such an exposure limit cannot be derived if the toxic action cannot be evaluated using a threshold model, as is the case for carcinogens acting by a stochastic genotoxic mechanism. In that case, an exposure-response relationship is recommended for use in regulatory standard setting, i.e., the calculation of so-called health-based calculated occupational cancer risk values (HBC-OCRVs). The Committee calculates HBC-OCRVs for compounds, which are classified as genotoxic carcinogens by the European Union or by the Committee as carcinogens in category 1A or 1B.

For the establishment of the HBC-OCRVs, the Committee generally uses a linear extrapolation method, as described in the Committee's report *Guideline for the calculation of occupational cancer risk values*.[1] The linear model to calculate occupational cancer risk is used as a default method, unless scientific data would indicate that using this model is not appropriate.

In the next phase of the three-step procedure, the Social and Economic Council advises the Minister of Social Affairs and Employment on the feasibility of using the HBC-OCRVs as regulatory occupational exposure limits. In the final step of the procedure, the Minister sets the official occupational exposure limits.

1.2 Committee and procedure

The present document contains the evaluation of the DECOS, hereafter called the Committee. The members of the Committee are listed at the end of this report.

In June 2018, the president of the Health Council released a draft of the report for public review. The Committee has taken the comments received into account in deciding on the final version of the report. These comments, and the reply by the Committee, can be found on the website of the Health Council.

1.3 Data

The Committee's recommendation has been based on scientific data, which are publicly available. Data were obtained from the online databases Toxline and Medline, using carcinogenic properties, carcino*, cancer, neoplastic, 1,2-dichloroethane and CAS registry number as key words. In addition, in preparing this report the following reviews were consulted: ATSDR (2001), IARC (1999), NTP (2011), OECD-SIDS (2002)

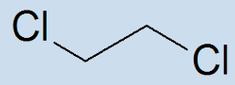
and WHO (1995).[2-6] The last literature search was performed in March 2018.

With respect to the carcinogenic mode of action, the Committee has requested the Subcommittee on Classification of Carcinogenic Substances for an evaluation of 1,2-dichloroethane. The advice of the Subcommittee can be found in Annex D.

02 identity, toxicity profile and classification

2.1 Identity and physical and chemical properties

1,2-Dichloroethane is used primarily to produce vinyl chloride. Physical and chemical data shown below are from http://toxnet.nlm.nih.gov (HSDB) (accessed April 14, 2016), ATSDR and IARC.[2,3]

Chemical name	:	1,2-dichloroethane
CAS number	:	107-06-2
EC number	:	203-458-1
IUPAC name	:	1,2-Dichloroethane
Synonyms	:	Ethylene dichloride, ethylene chloride, 1,2-bichloroethane, glycol dichloride, dichloroethylene, alpha-beta-dichloroethane
Physical description and colour	:	Clear, colourless oily liquid
Molecular formula	:	$C_2H_4Cl_2$
Structure	:	
Molecular weight	:	98.96
Melting point	:	-35.5 °C
Boiling point (101.3 kPa)	:	83.5 °C
Density (20°C)	:	1235 kg/m^3
Solubility	:	Solubility in water (20°C) = 8.7 g/L; Miscible with most organic solvents
Octanol/water partition coefficient, Log $P_{oct/w}$	:	1.48
Vapour pressure (20°C)	:	8 kPa
Relative vapour density (air = 1)	:	No data
Flash point	:	13°C (closed cup) 18 °C (open cup)
Odour threshold	:	20 mg/L (water); 12-100 ppm (air)
Conversion factor (20 °C, 101.3 kPa)	:	1 mg/m^3 = 0.25 ppm 1 ppm = 4 mg/m^3
EU classification (EC No 790/2009 of 10 August 2009)	:	Flam. Liq. 2: H225; Carc. 1B: H350; Acute Tox. 4: H302; Eye Irrit. 2: H319; STOT SE 3: H335; Skin Irrit. 2: H315

2.1 Toxicity profile

Information on the non-neoplastic effects of 1,2-dichloroethane have been summarised by the ATSDR (2001), IARC (1999), OECD-SIDS (2002), WHO (1995), and Gwinn et al. (2011).[2,3,5-7] A compilation of their reviews is given below. Additional information was found in the registration dossier on the ECHA website.[8] Additional literature is specified separately.

2.2.1 Kinetics and metabolism

1,2-Dichloroethane is rapidly and extensively absorbed through the lungs, gastro-intestinal tract and skin. Following absorption, 1,2-dichloroethane is distributed throughout all tissues of the body and is principally eliminated via biotransformation. A minor, yet significant fraction of the absorbed dose (<15%) is excreted as unchanged parent compound in exhaled air.[7] Metabolism appears to occur via two principal pathways, catalysed respectively by cytochrome P450 and by glutathione S-transferase. Cytochrome P450 enzymes catalyse oxidative transformation of 1,2-dichloroethane to 2-chloroacetaldehyde, 2-chloroacetic acid and 2-chloroethanol, which are conjugated both enzymatically and non-enzymatically with glutathione (GSH). The other pathway involves direct conjugation with GSH to form S-(2-chloroethyl)glutathione.[3]

Metabolism of 1,2-Dichloroethane occurs rapidly with a reported elimination half-life of 20-30 min in male Osborne-Mendel rats following inhalation and oral dosing, with the majority of elimination attributed to metabolism.[7]

While activation of 1,2-dichloroethane through the oxidation pathway (by CYP450) may play a role in chromosomal aberrations, the glutathione conjugation pathway appears to be the predominant 1,2-dichloroethane mutagenicity pathway.[7]

2.2.2 Acute toxicity

Human data

Several cases of acute exposures to humans have been reported in the literature. Accidental ingestion of 15-60 mL of 1,2-dichloroethane has been reported to cause death within 10-28 hours of exposure. Several of these deaths have been attrib-uted to circulatory or respiratory failure. Exposure to concentrated 1,2-dichloroethane vapour for 30 minutes resulted in cardiac arrest and death 5 days after exposure.

Animal data

The LD50 for oral exposure ranged from 770-967 mg/kg bw in rats, 413-911 mg/kg bw in mice, and approximately 910 mg/kg bw in rabbits. In dogs a LD50 of >2,500 mg/kg bw was observed. Non-lethal effects observed included congestion of the lungs, pale kidneys and livers, and congestion of blood vessels in the intestines. LC50 values of rats after inhalation exposure ranged from approximately 4,000 mg/m^3 after 7 hours of exposure to > 49,000 mg/m^3 after 30 minutes exposure. In mice (6-hour exposure) and guinea-pig (7-hour exposure) a LC50 of 1,080 mg/m^3 and 6,400 mg/m^3, respectively, have been observed. In these studies several adverse effects have been reported including liver and kidney damage, pulmonary and visceral congestion. A dermal LD50 of 4,890 mg/kg bw has been observed after 24 hours occluded application.

2.2.3 Irritation/sensitisation

Irritation studies demonstrated that 1,2-dichloroethane is irritating to the skin and eye. A mouse local lymph node assay (OECD 429, GLP) indicated that the substance is not a skin sensitiser.

2.2.4 Repeated dose toxicity

Human data

Repeated exposure in humans has been associated with various effects including respiratory and haematological effects, nausea, vomiting, abdominal pain, dysfunction of liver and kidney, and neurological disorders.

Animal data

Effects on non-cancer endpoints upon chronic exposure to 1,2-dichloroethane were reported for several of the carcinogenicity studies summarised in Table 4 (Annex B). in addition, results of relevant sub-chronic studies are summarised below.

Inhalation

In a two-year inhalation study by Nagano et al. (1998/2006), in which mice and rats were exposed for 6 hours per day, 5 days a week, no exposure-related changes in the incidence of any haematological, blood biochemical or urinary parameter occurred in mice (40, 120, 360 mg/m^3) and rats (40, 160, 640 mg/m^3).[9,10] There was no significant difference in survival rate, body weight and food consumption in males of both species and in female rats. In female mice, increased mortality at the mid-concentration was attributed to the significantly increased malignant lymphoma deaths. This mortality was not ascribed to treatment. Incidences of subcutaneous masses, which were found in the breast, back, and abdominal and perigenital areas were increased in the exposed groups.

In a study by Cheever et al. (1990) rats were exposed to 200 mg/m^3 1,2-dichloroethane by inhalation 7 hours a day, 5 days a week for 2 years.[11] No substance-related effects were observed on mortality, body weight, and food and water consumption. The extensive histopathology investigation showed no adverse effects, except increased testicular lesions in 10 and 24% of the control and exposed rats, respectively.

As part of a chronic inhalation study by Maltoni et al. (1980), Spreafico et al. (1980) investigated the effect of 1,2-dichloroethane on clinical chemistry parameters.[12,13] Rats were exposed to 20, 40, 200, or 600-1,000 mg/m^3 1,2-dichloroethane for 7 hours per day, 5 days per week for 78 weeks. The dose of the 1,000 mg/m^3 dose group was reduced to 600 mg/m^3 after a few weeks because of the high toxicity and deaths that were observed. No consistent exposure-related effects on haematological parameters and clinical chemistry parameters were measured after three, six, 12 or 18 months of exposure.

Oral exposure

In the oral exposure study by the National Cancer Institute (NCI), no dose-related mean body weight depression was apparent in rats.[14-16] From week 6 of the study, several rats in both treated groups (47 and 95 mg/kg bw/day) showed a hunched appearance and transient laboured respiration, abdominal urine stains, cloudy or squinted eyes, or eyes with a reddish crust. The incidence of palpable nodules and/or tissue masses was slightly greater in the treated than in the control animals. In mice, mean body weight depression was observed for high dose females (299 mg/kg bw/day). Palpable nodules and/or tissue masses and swelling around the abdominal midline were observed with slightly greater frequency in the treated groups than in the controls. An overall high mortality in both rats and mice in the exposed groups was present, possible due to carcinogenicity.

The toxicity of 1,2-dichloroethane after repeated oral exposure has also been investigated by the NTP. Three rat species (F344/N, Sprague-Dawley, Osborne-Mendal) and the B6C3F1 mice were exposed for thirteen weeks via drinking water to concentrations of 0, 500, 1,000, 4,000, 8,000 ppm 1,2-dichloroethane (corresponding for rats to doses between 50-730 mg/kg bw/day). Weight gain depression in each sex of all three rat

strains in the 4,000 and 8,000 ppm groups was observed. Water consumption decreased by 50-60% with increasing dose for all exposed male and female rats. Kidney and liver weight increased in dosed rats of all strains. No treatment-related lesions were observed except for a dose-related increase in the incidence of renal tubular regeneration in female F344/N rats. Nine out of ten female mice exposed to 8,000 ppm (corresponding to about 4,200-4,900 mg/kg bw/day) died before the end of the study. Mean body weights of male mice exposed to 500 ppm 1,2-dichloroethane or more and female mice exposed to 1,000 ppm or more were lower compared to the controls. Kidney weights were significantly increased for these male and female mice. Renal tubular cell regeneration was seen in male mice at 8,000 ppm.[17,18]

In the same study an extra group of F344/N rats received the substance via oral gavage (males: 0, 30, 60, 120, 240, 480 mg/kg bw/day; females: 0, 18, 37, 75, 150, 300 mg/kg bw/day). All male rats exposed to 240 or 480 mg/kg bw/day and 9/10 females that received 300 mg/kg bw/day died before the end of the study. Mean body weights of the highest dose males and females were lower compared to the control. Liver and kidney weights were increased for dosed males and females. Necrosis of the cerebellum, hyperplasia, inflammation, and mineralization of the forestomach were seen in animals that died or were killed in moribund condition.[17,18]

2.2.5 Reproduction toxicity

1,2-Dichloroethane is not classified for reproduction toxicity.

ATSDR (2001) and IARC (1999) reviewed a several reliable developmental toxicity studies in which female rabbits and rats were exposed to 1,2-dichloroethane during pregnancy.[2,3] In one study the animals were exposed by inhalation for 7 hours/day on gestation days 6-18 (rabbit) or 6-15 (rat) at concentrations of 100 or 300 ppm (400 or 1,200 mg/m^3). At 400 mg/m^3 no adverse effects on the dam or the offspring were observed. Exposure of rats to 300 ppm resulted in high maternal mortality, foetolethality, and resorption of all implantations in one dam. In rabbits, 1,200 mg/m^3 was lethal to some dams but there were no foetotoxic or teratogenic effects observed. In another inhalation study in rats, exposure up to 300 ppm (1,200 mg/m^3, 6 hours/day on gestation days 6-20) induced no embryo- or foetotoxicity, changes in foetal growth or teratological effects while maternal weight gain was decreased at the highest concentration. Treatment of rats by gavage on gestation days 6-20 at 198 mg/kg body weight resulted in reduced weight gain of the dams and embryolethal effects (increased non-surviving implants and resorptions sites per litter) but no foetotoxicity or teratogenicity. At the next lower dose of 158 mg/kg body weight these effects did not occur. Possible developmental effects, including fetal visceral or skeletal malformations, were also examined in a 2-generation reproduction toxicity study in mice exposed via the drinking water (see next paragraph for dose levels). No substance-related effects on the offspring were observed.

ATSDR and IARC described two reliable reproduction toxicity studies.[2,3]

A study in rats showed no adverse effects on reproductive performance or

development (until postpartum day 21) upon exposure by inhalation (6 hours/day) at concentrations up to 150 ppm (600 mg/m^3) for 60 days pre-mating on five days/week, and then on 7 days/week throughout mating, gestation and lactation (excluding gestation day 21 through postpartum day 4). Similarly, no effects on reproductive performance or development were found in a 2-generation study in mice which were exposed via the drinking water at concentrations up to 290 mg/L (intended to provide daily doses up to 50 mg/kg body weight) starting five weeks before mating of the F0 generation. In addition, ATSDR[1] describes inhalation studies in rats which showed embryomortality (exposure to 4.7 ± 7 ppm (19 ± 28 mg/m^3) for 4 months prior to mating and during gestation) or decreased fertility and increased stillbirths and perinatal mortality (exposure to 14 ppm (57 mg/m^3) for 6 months). However, the reliability of these studies is unclear because of deficiencies in reporting study design and results.

Based on the above results, the Committee concludes that there is no convincing evidence that 1,2-dichloroethane adversely affects reproduction at doses below those which cause other systemic effects.

2.2.6 Genotoxicity

Studies investigating the mutagenicity/genotoxicity of 1,2-dichloroethane have been reviewed by the IARC (1999), ATSDR (2001), WHO (1995) and Gwinn et al. (2011).[2,3,6,7] A summary based on these reviews is given below, specific literature is referenced separately.

Genotoxicity refers to the ability of a substance to induce mutations and/or chromosomal aberrations. Indicator tests can be informative, but in contrast to a genotoxicity test, do not allow conclusions on genotoxicity as results do not provide information on permanent, heritable genetic changes.

Human data

One study on the genotoxicity of 1,2-dichloroethane in humans is available. In this study, sister chromatid exchange (SCE) frequency was determined in 51 men employed in two vinyl chloride monomer manufacture plants.[19] These workers had increased SCE frequencies when compared to 20 office workers who were assumed to have no 1,2-dichloroethane exposure. The authors concluded that an increase in SCE was associated with moderate exposure levels (around 1 ppm) of 1,2-dichloroethane, but not vinyl chloride monomer.

In vitro data

Mutagenicity assays

Several in vitro mutagenicity studies in non-mammalian cells have been performed. In general, 1,2-dichloroethane was found to be not mutagenic in the *Salmonella typhimurium* strains which detect frame-shift mutations (TA 98, TA 1537 and TA 1538) in the absence and presence of exogenous metabolic activation, but mutagenicity was observed in the base-pair

substitution strain TA100 and TA1535 after exogenous metabolic activation. No mutagenicity was observed in *Escherischia coli* and in fungal systems. Mutagenicity was also observed in Chinese hamster ovary cells and in human lymphoblastoid cell lines AHH-1 and TK6.

Cytogenicity assays

Micronuclei were induced in AHH-1 cells in vitro without exogenous metabolic activation.

Indicator tests

1,2-Dichloroethane induced unscheduled DNA synthesis in the absence of exogenous metabolic activation (mouse and rat hepatocytes) and in the presence of exogenous metabolic activation (human peripheral lymphocytes). DNA binding was observed in calf thymus DNA with and without exogenous metabolic activation and to mouse hepatocytes without exogenous metabolic activation.

In vivo data

Mutagenicity assays

Hachiya et al. (2000) tested the potential of 1,2-dichloroethane to induce *lacZ* mutations in the liver and testis of transgenic mouse model.[20] Animals were given either a single injection of 75 or 150 mg/kg bw, or multiple injections up to total dose of 280 mg/kg bw). The liver and testes were collected 7, 14, and 28 days after the last treatment, DNA was isolated and lacZ mutant frequency was determined. No increase in mutant frequency was detected.

In a mouse spot test, the number of somatic gene mutations in progeny of mice exposed to 300 mg 1,2-dichloroethane/kg on gestational day 10 was increased when compared to all controls (p=0.03) but not when compared to the vehicle controls.[21] Only one dose was tested.

Cytogenicity assays

Results of four micronucleus tests in mice are available, which were all negative. In a bone marrow micronucleus test with NMRI mice, two doses of 396 mg/kg injected i.p. 24h apart did not result in an increased induction of micronuclei at 6h after the last injection.[22] Also no increase of micronuclei was measured in peripheral blood in Eμ-PIM-1 transgenic mice treated orally with doses up to 300 mg/kg bw/d for 41 weeks[23], in CD-1 mice 24-48h after a single i.p. injection of 188-376 mg/kg[24], or in a B6C3F1 mice exposed to 1,2-dichloroethane concentrations up to 8,000 ppm in water for 90 days[25]. In a recent genotoxicity study by Lone et al. (2016), male rats were exposed to 80.7, 161.4 or 242.1 mg/kg bw. At 24h and 48h, induction of micronuclei and chromosomal aberrations were detected in the bone marrow.[26] Negative results were observed in a dominant lethal test in ICR Swiss mice after 7 daily oral doses of 50 mg 1,2-dichloroethane/kg bw.[27] Positive results, however, are available from a

sister chromatid exchange assay in ICR Swiss mice, 24h after i.p. exposure to doses up to 16 mg/kg bw.[28]

Indicator tests

DNA single strand breaks were induced in B6C3F1 mice liver after oral and intraperitoneal exposure[29,30], but not after inhalation (500 ppm (2,000 mg/m^3), 4h)[30]. In one study with CD-1 mice treated with 200 mg/kg i.p., stomach, kidney, bladder, lung, brain and bone marrow were also analysed and single strand DNA breaks were detected.[31] DNA strand breaks were also observed in CD rat liver[32] and rat bone marrow[26] after oral exposure.

In an unpublished study summarised in the ECHA registration dossier, a Comet assay was performed in mammary gland tissue of female rats, exposed to 0 or 200 ppm (800 mg/m^3) of 1,2-dichloroethane vapour for 28 consecutive days (28-31 exposures).[33] No DNA damage was detected. In this study, formation of DNA adducts in mammary tissue and liver tissue was also assessed. No increase in 8-hydroxy-2'-deoxyguanosine adduct levels in mammary tissue was observed, whereas the respective levels in the liver of exposed rats were significantly less than control rats. Endogenous S-[2-(N7-guanyl)ethyl]glutathione adduct was not quantifiable in mammary or liver tissue isolated from control rats. In 1,2-dichloroethane-exposed animals, a statistically significant increase in S-[2-(N7-guanyl) ethyl]glutathione adduct levels was observed in both mammary tissue and liver tissue (with approximately ~54% higher levels in liver tissue than in mammary tissue).

In vivo, increased formation of DNA adducts following exposure to 1,2-dichloroethane has also been shown after i.p. injection in rats and mice[34-36], and after inhalation exposure in rats.[37] Also, the ability to bind DNA was observed in liver, lung, stomach, and kidney of mice after intraperitoneal injection and to the same organs of rats after inhalation, oral exposure and intraperitoneal injection.

Conclusions on genotoxicity

Based on the recommendation of the Subcommittee, the Committee concludes that 1,2-dichloroethane is a stochastic genotoxic carcinogen and applies a risk-based approach for the hazard quantification. The advice of the Subcommittee can be found in Annex D.

2.3 Existing occupational exposure limits

Table 1 summarizes the occupational exposure limits established by the regulatory authorities of the Netherlands, the United Kingdom, Denmark, Sweden and by the USA-ACGIH, USA-NIOSH and USA-OSHA.

Table 1. Occupational exposure limits of 1,2-dichloroethane

Country (Organization)	OEL[a] (ppm)	OEL (mg/m^3)	TWA	Type of exposure limit
The Netherlands[a]	-	7	8h	OEL
UK (HSE)[a]	5	21[d]	8h	WEL
Denmark[a]	1	4[d]	8h	OEL
Sweden[a]	1	4[d]	8h	OEL
Sweden[a]	5	20[d]	15 min	OEL
USA (ACGIH)[b]	10	40	8h	TLV
USA (NIOSH)[c]	1	4	8h	REL
USA (NIOSH)[c]	2	8	15 min	REL
USA (OSHA)[c]	50	-	8h	PEL

Abbreviations: OEL: occupational exposure limit; PEL: permissible exposure limit; REL: recommended exposure limit; TLV: threshold limit value; TWA: time-weighted average [a]www.ser.nl, [b]www.epa.com, [c]www.cdc.gov, [d]skin notation

2.4 Classification as a carcinogenic substance

The European Union has classified 1,2-dichloroethane as a category 1B carcinogen (*presumed to have carcinogenic potential for humans*). IARC has classified the compound as a group 2B carcinogen (*possibly carcinogenic to humans*).[3]

03 carcinogenicity studies

3.1 Human studies

The Committee identified 14 epidemiological studies investigating mortality or cancer incidence among chemical workers or residents potentially exposed to 1,2-dichloroethane. These studies are briefly described below. More details on the occupational studies are given in Table 2 and 3 of Annex A.

Cohort studies

In a cohort of male employees of a petrochemical plant, conducted to investigate a cluster of brain tumours reported earlier in this population, insufficient evidence was found to conclude that these tumours were occupationally related.[38,39] Another investigation of brain tumours among chemical plant employees, using a sample-based cohort method, suggested at most a slight increased risk of mortality from brain tumours for the overall time period, and a probable elevated risk associated with first employment prior to 1945.[40]

Excess mortality from tumours (total tumours, stomach cancer and leukaemia) was found in a cohort of males working in ethylene oxide production.[41] Excess mortality from pancreatic cancer and from lymphatic and haematopoietic cancers was found in a cohort of male chlorohydrin production workers.[42] Examination of another cohort of male chlorohyrin production workers showed no increased risk of these cancer (pancreatic, lymphopoietic) or of any other malignancies.[43] Further, no excess mortality from cancer or other causes was found in a cohort of males employed at a chemical plant.[44]

Case-control studies

An increased risk (odds ratio) was observed for primary breast cancer in men employed in trades with potential exposure to gasoline and its combustion products (which might contain 1,2-dichloroethane) and for pancreatic cancer in white men and women with a high probability of occupational exposure to 1,2-dichloroethane.[45,46] No increased risk associated with 1,2-dichloroethane was found for primary brain tumours among workers of a petrochemical plant, for soft-tissue sarcoma among employees of a multi-chemical production plant, or for renal cell carcinoma among men and women exposed to organic solvents.[47-49]

Studies on associations of environmental factors with cancer

Isacson et al. investigated possible associations between cancer incidence rates of municipal residents and the level of certain volatile organic contaminants and metals in finished public drinking water supplies.[50] The results showed a statistically significant association between the presence of detectable 1,2-dichloroethane (≥ 0.1 µg/L) and the incidence rates of colon cancer and rectal cancer in males. This association could not be explained by occupational or other sociodemographic features including smoking. Data from this study do not permit conclusions on specific water quality variables which may be associated with risk of human cancer.

The results of a study by Goldberg et al. suggest that there may be increased risks for cancers of the stomach, liver, lung, prostate and cervix uteri among persons who live near a solid waste site which emitted airborne 1,2-dichloroethane (among other chemicals).[51] Because of the unavailability of exposure data and inadequate control of potentially confounding factors, it cannot be concluded whether the observed excess cancer risks represent true associations with exposure to chemicals released from the waste site.

The Committee considers the epidemiological data not suitable for hazard quantification, due to limitations in study design (in particular because of the presence of co-exposures and the lack of quantitative exposure information).

3.2 Animal experiments

In Table 4 (Annex B) carcinogenicity studies performed with experimental animals are summarized. The summarized studies comprise five inhalation studies of which three were performed with rats and two with mice. One oral study in mice and one in rats were performed. Furthermore, one study with intra-peritoneal injections and two using dermal applications were available.

Nagano et al. (1998/2006) performed an inhalation carcinogenicity study with F344 rats and BDF1 mice.[9,10] Rats were exposed to 0, 40, 160, and 640 mg/m^3 1,2-dichloroethane for 6 hours/day, 5 days/week for a maximum of 104 weeks. In male rats the incidence of mammary gland fibroadenoma was statistically increased in the high dose group ($p<0.05$). In female rats subcutis fibroma, mammary gland adenoma and fibroadenoma were statistically significantly increased in the high dose group ($p<0.05$). Further, dose-dependent increases in the incidences of subcutis fibroma and peritoneum mesothelioma in male rats and of adenocarcinoma in female rats were reported (significant positive trend by Peto's test), but the incidences in individual exposed groups did not differ statistically significantly from the concurrent control incidence.

In the mouse study of Nagano et al. the animals were exposed to 0, 40, 120, 360 mg/m^3 for 6 hours/day, 5 days/week for a maximum of 104 weeks. In female mice, a significant positive trend (Peto's test) was observed for the incidences of bronchio-alveolar adenomas and carcinomas in the lung, endometrial stromal polyps in the uterus, adenocarcinoma in the mammary gland, and hepatocellular adenomas. Though the incidences of these tumours did not attain statistical significance compared with concurrent controls, they exceeded the maximum historical control incidence (exception: carcinoma in the lung) and were ascribed to treatment. The statistically significant increases (compared to concurrent controls) in the incidences of malignant lymphomas in the lymph node of female mice of the low- and mid-dose groups were not likely to be related to treatment because there was no concentration-related response and the incidences in all exposed groups were in the historical control range whereas the concurrent control incidence was lower than observed histori-

cally. In male mice of the mid- and high-dose groups the incidence of liver hemangiosarcoma was statistically significantly increased compared with concurrent controls. This finding is not likely to be causally related to treatment because there was no significant dose-response relationship and the incidence in the high-dose group was in the historical control range.[9,10]

In a study, performed by the NCI, the carcinogenicity of 1,2-dichloroethane using Osborne-Mendel rats (50 animals/sex/exposed group) was determined. 1,2-dichloroethane in corn oil was administered by gavage in time weighted average (TWA) exposure doses of 0, 47, or 95 mg/kg bw/day for 78 weeks. 20 animals/sex received vehicle treatment and 20 animals/sex were left untreated. All surviving animals were sacrificed at 110 weeks.

A statistically significant positive association between dosage and incidence of squamous-cell carcinoma of the forestomach and hemangiosarcomas of the circulatory system occurred in the male rats. There was also a significantly increased incidence of adenocarcinomas of the mammary gland in female rats.[14-16]

In the same study by the NCI the substance was also tested on $B6C3F_1$ mice (50 animals/sex/exposed group) by gavage by exposing mice to a TWA of 0, 97, 195 mg/kg bw/day for male mice and 0, 149, 299 mg/kg bw/day for female mice for 78 weeks. 20 animals/sex received vehicle treatment and 20 animals/sex were left untreated. All surviving animals were sacrificed at 91 weeks. The incidence of mammary adenocarcinoma was statistically significantly increased in female mice exposed to 1,2-dichloroethane. The incidence of alveolar/bronchiolar adenomas in both exposed male and female mice were also statistically significant increased compared to control.[14-16]

In a study performed by Maltoni et al. (1980/1982) Sprague-Dawley rats and Swiss mice were exposed to 1,2-dichloroethane via inhalation to concentrations of 20, 40, 200 or 600-1,000 mg/m^3 for 7 hours/day, 5 days/week, for 78 weeks.[12,52] Concurrent control mice and one group of control rats were kept in a nearby room. An additional control group of rats was kept in an exposure chamber under the same conditions as exposed rats. Tumour incidences in exposed animals did not differ from control incidences, except for benign mammary tumours (fibromas and fibroadenomas combined) in female rats. The incidence of these mammary tumours was statistically significantly increased at 20, 200 and 600-1,000 mg/m^3 compared with controls kept in an exposure chamber but not compared with controls in a nearby room (the incidences in the two control groups differed significantly). There was no dose-related response (the highest incidence was observed at the lowest concentration tested). Moreover, the onset of fibromas and fibroadenomas is known to be age-correlated. Therefore, the intergroup differences in mammary tumour incidence probably reflected intergroup differences in survival rather than an effect of treatment.

In addition, four other carcinogenicity studies have been identified by the Committee, but these studies were considered to be less adequate for carcinogenicity assessment due to multiple deficiencies.

Cheever et al. (1990) exposed Sprague-Dawley rats by inhalation to 0 or 200 mg/m^3 1,2-dichloroethane for 7 hours/day, 5 days/week, for 2 years.[11] All tumour incidences found in the exposed rats were similar to the control group.

In a study by Van Duuren et al. (1979) groups of 30 female Ha:ICR Swiss mice received thrice-weekly skin application of 42 or 126 mg 1,2-dichloroethane per animal in 0.2 ml acetone or acetone alone on the shaved dorsal skin.[53] The highest dose showed a significantly increased incidence of lung papilloma ($p<0.0005$) compared to controls (0.1 mL acetone).

Suguro et al. (2017) tested the carcinogenic potential of dermally applied 1,2-dichloroethane in rasH2 transgenic mice (strain CB6F1-TG (rasH2), containing approximately three copies of the human c-Ha-ras proto-oncogene).[54] Animals (males and females) were treated 3 times a week for 26 weeks with 126 mg/mouse in acetone. The incidences of bronchiolo-alveolar adenomas and adenocarcinomas were increased in both sexes; bronchiole-alveolar hyperplasias were increased in female mice.

Theiss et al. (1977) studied the formation of lung adenoma in male A/St mice after intra-peritoneal injections (0, 20, 40, 100 mg/kg) three times a week for eight weeks.[55] Twenty-four weeks after the first injection, the mice were sacrificed. The number of lung adenomas and the average of lung tumours per mouse was comparable between the exposed group and controls.

3.3 Selection of the suitable study for risk estimation in the occupational situation

The Committee prefers the use of epidemiological data, however, no suitable data are available. Therefore, the Committee has focused on animal carcinogenicity data. The main route of occupational exposure to 1,2-dichloroethane is inhalation of its vapour. Therefore, occupational cancer risk values are preferably derived from inhalation studies. The inhalation studies in rats and mice by Maltoni et al. (1980/1982)[12,52] and the rat inhalation study by Cheever et al. (1990)[11] are not suitable for derivation of cancer risk values because these studies showed no substance-related increase in the incidence of any malignant tumour. In the more recent studies by Nagano et al. (1998/2006)[9,10] 1,2-dichloroethane induced a dose-dependent increase in the incidences of benign and malignant tumours in various organs in both rats and mice. The inhalation studies of Nagano et al. are well-performed, the exposure period covered the largest part of the standard lifespan of the experimental animals, and groups sizes were adequate (individual animal data were not reported).

Substance-related increases in benign and malignant tumours were also observed in rats and mice administered 1,2-dichloroethane via the oral route (gavage).[14-16] These oral studies, conducted by NCI, are also adequate for cancer risk assessment. However, as the inhalation route is most relevant for occupational exposure to 1,2-dichloroethane, the

Committee prefers to use the inhalation studies by Nagano et al. for derivation of the occupational cancer risk values.

In the inhalation studies by Nagano et al., 1,2-dichloroethane induced a slight increase in the incidence of mammary gland adenocarcinomas in both female mice and female rats at the highest concentration tested (i.e. 360 mg/m^3 in mice and 640 mg/m^3 in rats). This type of malignant tumour is relevant for humans. The malignant tumours induced by 1,2-dichloroethane at sites other than the mammary gland (i.e. peritoneum mesotheliomas in male rats and lung bronchio-alveolar carcinomas in female mice) are not relevant for humans. Though the increase in mammary gland adenocarcinomas was not statistically significant compared to concurrent controls, the incidences exhibited a statistically significant positive trend and the maximum incidence in historical controls was exceeded. Therefore, the Committee considers the slight increase in the incidence of mammary gland adenocarcinomas biologically significant and related to treatment. The mouse study was selected for cancer risk derivation, because the mouse developed mammary tumours at a lower exposure level than the rat.

In its previous evaluation of 1,2-dichloroethane (published in 1997)[56] the Committee calculated cancer risk values on the basis of the incidence of haemangiosarcomas in male rats in the oral carcinogenicity bioassay conducted by NCI.[14-16] This oral study was considered most suitable because the inhalation studies available at that time showed no substance-related increases in tumour incidences. The inhalation studies of Nagano et al. (1998/2006) were not yet available at the time of the previous evaluation.[9,10]

3.4 Calculation of the HBC-OCRV

To calculate the carcinogenic activity expressed as the incidence per unit air concentration (mg/m^3) of 1,2-dichloroethane, the number of female mice with mammary gland adenocarcinomas was used as starting point. The Committee is of the opinion that the available data do not indicate that the use of linear extrapolation is inappropriate and that the data are adequate to use the benchmark dose (BMD) method for estimation of the starting point for calculation of the carcinogenic activity. The Committee prefers the benchmark dose (BMD) method for estimation of the starting point for calculation of the carcinogenic activity. Until recently, the Committee used the BMDS software by U.S. EPA. The Committee has decided to use the PROAST software, which is developed by the RIVM and made available by EFSA. PROAST provides model averaged BMDL and BMDU values, taking into account all models, from which a weighted BMD can be derived. This analysis takes into account all possible values of the true BMD based on the available data, and is therefore used for calculation of the HBC-OCRV. The results of these BMD-analyses and the criteria for model fit are given in Annex C.

The incidence per unit concentration in air (mg/m^3) (lifespan conditions, assuming a linear concentration-response relationship) is calculated as follows:

$$I_{concentration} = \frac{BMR}{BMD \quad \frac{Xpo}{L} \times \frac{Xpe}{L} \times \frac{\text{exposure hours per day}}{24} \times \frac{\text{exposure days per week}}{7}} =$$

$$\frac{0.1}{366 \times \frac{728}{750} \times \frac{728}{750} \times \frac{6}{24} \times \frac{5}{7}} \quad 1.63 \times 10^{-3} \text{ per mg/m}^3$$

Where:

- $I_{concentration}$ = the carcinogenic activity attributable to the exposure to the substance per unit concentration in air expressed per mg/m^3
- BMR = benchmark response, expressed as an increase in tumour incidence of 10%
- BMD = benchmark dose (estimate of concentration in air expected to yield the BMR)
- X_{po} and X_{pe} are the exposure and experimental periods, respectively
- L = standard lifespan for the animals in question (lifespan mouse is assumed to be 750 days)

To estimate the additional lifetime risk of cancer in humans under lifespan conditions on the basis of results in animal experiments, it is assumed that no difference exists between experimental animals and man with respect to toxicokinetics, mechanism of tumour induction, target, susceptibility etc. Furthermore, it is assumed that the average man lives 75 years, is exposed 24 hours per day, 7 days per week, 52 weeks per year for lifetime and inhales 18 m^3 air per 24 hours. To estimate the additional lifetime risk of cancer in humans under workplace exposure conditions it is further assumed that the average worker is exposed 8 hours per day, 5 days per week, 48 weeks per year for 40 years and inhales 10 m^3 air per 8-hour working day.

Using as starting point the estimated incidence of 1.65 x 10^{-3} per mg/m^3 bw, the additional life-time cancer risk per mg/m^3 under occupational exposure conditions (= HBC-OCRV) amounts to:

$$HBC - OCRV = 1.63 \times 10 - 3 \times \frac{40y}{75y} \times \frac{48w}{52w} \times \frac{5d}{7d} \times \frac{10m^3}{18m^3} = 3.18 \times 10^{-4} \text{ per mg/m}^3$$

Based on the HBC-OCRV of 3.18 x 10^{-4} per mg/m^3, the Committee estimated that the concentration of 1,2-dichloroethane in the air, which corresponds to an excess cancer mortality of:

- per 1,000 (4 x 10^{-3}), for 40 years of occupational exposure, equals to 12.6 mg/m^3
- per 100,000 (4 x 10^{-5}), for 40 years of occupational exposure, equals to 0.126 mg/m^3.

Recently, SCOEL also published a report on 1,2-dichloroethane in which cancer risk estimates of 6.3 and 0.063 mg/m^3 were proposed, corresponding to risk levels of 4 x 10^{-3} and 4 x 10^{-5}, respectively.[57] The Committee notes that SCOEL used the same study (Nagano et al., 2006)[10] as the Committee and applied comparable methods for these

estimates. However, the Committee has based its calculations on the number of adenocarcinomas in the mammary gland of the female rat, whereas SCOEL used the number of both mammary gland adenoma and fibro- adenomas.

The toxicity data as summarized in this report allow the Committee to conclude that no adverse effects other than carcinogenicity at the concentration levels associated with the target and prohibitive cancer risk levels are expected.

3.5 Skin notation

To determine whether a skin notation needs to be applied, the Committee uses the ECETOC criteria for assigning a skin notation.[58] According to the guidance a skin notation should be applied when exposure of 2,000 cm^2 of skin (both hands and forearms) to 1,2-dichloroethane during one hour could result in an absorbed amount exceeding 10% of the amount that can be absorbed via the lungs on exposure for eight hours to the occupational exposure limit (HBC-OCRV).

Skin penetration data for human skin in vitro is available in the disseminated dossier on the ECHA website.[8] The neat material (5, 10, 25 and 100 µl/cm^2) and aqueous solutions (200 µl/cm^2) of 1,2-dichloroethane were applied to human epidermal membranes. The absorption rate of the aqueous solution of 1,2-dichloroethane through the epidermal membranes was 25.8 µg/cm^2/h after 15 minutes and 20.3 µg/cm^2/hr after 1 hour. For the absorption of the neat material an absorption rate of 106 µg/cm^2/h was observed after 15 minutes, while after one hour the absorption rate was increased to 205 µg/cm^2/h. Depending on the exposure conditions, the uptake of 1,2-dichloroethane ranges between 20.3 and 205 µg/cm^2/h. This corresponds to an hourly absorption of 40.6 to 410 mg for a skin surface of 2000 cm^2.

Assuming that a volume of 10 m^3 is inhaled in 8 hours and that a fraction (by default assumed to be 0.5 by ECETOC) of the atmospheric 1,2-dichloroethane is absorbed by inhalation, the maximum uptake by inhalation upon exposure for 8 hours at the HBC-OCRV is:

- 12.6 mg/m^3 (HBC-OCRV, 4 x 10^{-3}) x 10 m^3 x 0.5 = 63 mg (10% hereof is 6.3 mg)
- 0.126 mg/m^3 (HBC-OCRV, 4 x 10^{-5}) x 10 m^3 x 0.5 = 0.63 mg (10% hereof is 0.063 mg).

Based on these calculations, the Committee concludes that dermal exposure can considerably contribute to the systemic exposure to 1,2-dichloroethane and that a skin notation for 1,2-dichloroethane is required.

3.6 Groups with increased risk

The Committee identified no groups with increased risk.

3.6 Conclusions and recommendation

The Committee is of the opinion that 1,2-dichloroethane is a human carcinogen and that a stochastic genotoxic mechanism underlies its carcinogenicity.

The Committee considers the increase in mammary gland adenocarcinomas in the mouse as the critical effect and selected the mouse study from Nagano et al. for cancer risk derivation.[9,10]

The Committee estimates that the concentration of 1,2-dichloroethane in the air, which corresponds to an excess cancer mortality of:

- 4 per 1,000 (4×10^{-3}), for 40 years of occupational exposure, equals to 12.6 mg/m^3
- 4 per 100,000 (4×10^{-5}), for 40 years of occupational exposure, equals to 0.126 mg/m^3.

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annexes

A epidemiological studies

Table 2. 1,2-Dichloroethane, cohort studies

Reference	Study design and population	Data on exposure and health assessment	Results	Remarks
Hogstedt et al., (1979)[41]	Type of study: Retrospective cohort mortality and cancer incidence study. Country: Sweden. Type of industry: ethylene oxide production. Participants: male employees of a company producing ethylene oxide by chlorohydrin-process; 3 subcohorts: 89 full-time exposed, 86 intermittently exposed, 66 who had never worked in ethylene oxide production. Follow-up period: 1961-77.	Rough estimates of exposure levels to various compounds based on investigation of production processes. Cause of death from death certificates. Diagnosis for malignancies in dead or alive subjects from Swedish Cancer Registry. Expected numbers of deaths and malignancies calculated from national statistics. Statistical analysis: p values based on Poisson distribution.	Full-time exposed cohort: excess total mortality, mainly due to increased mortality from tumours (significant excess of stomach cancer and leukaemia) and circulatory system diseases; Intermittently and non-exposed cohorts: no excess total mortality or mortality from tumours.	Workers potentially exposed to multiple (carcinogenic) chemicals.
Reeve et al. (1983)[40]	Type of study: Retrospective, sample-based cohort mortality study. Country: USA. Type of industry: petrochemical plant. Participants: 25 brain tumour deaths in white males, identified by a geographically limited record-linkage process. Control: expected brain tumour deaths extrapolated from 1,666 white males in a 5% sample of the 1940-77 total workforce.	No information on exposure levels. Sample-based standardized mortality ratios (SMRs) were calculated from observed and expected brain tumour deaths. Statistical analysis was not performed. Work histories and smoking status were not taken into account.	SMRs suggest, at most, only a slight increased risk of mortality from brain tumours for the overall time period, and a probable elevated risk associated with first employment prior to 1945.	Workers potentially exposed to multiple chemicals. No quantitative exposure data and no data on individual chemicals. Validity of assumptions underlying the modified study design not tested.

Reference	Study design and population	Data on exposure and health assessment	Results	Remarks
Austin and Schnatter (1983); Teta et al. (1991)[38,39]	Type of study: Retrospective cohort mortality study. Country: USA. Type of industry: petrochemical plant. Participants: Initial study: all 6,588 white males who worked at the plant for >1 day in the period 1941-77; Update: 7,849 white and non-white men who worked at the plant for >1 day between 1941-83. Control: expected mortality values based on national rates.	No information on exposure levels. Production job assignments categorized to one of 15 work areas (including a 1,2-dichloro-ethane area); maintenance job assignments were assigned to one of eight categories. Study focused on malignant brain neoplasms. Overall and cause-specific standardized mortality ratios (SMRs) and confidence intervals (CI) were calculated for various subgroups. Appropriate statistical analysis was performed. Work histories and smoking status were not taken into account.	Mortality: Initial study: All causes (p<0.05): Observed 765, SMR 83 (CI 77-89); All malignant neoplasms: Observed 158, SMR 86 (73-101), not significant; Malignant neoplasms brain and CNS: Observed 12, SMR 162 (83-283), not significant. Insufficient evidence to conclude that brain tumours were occupationally related. Update: Between 1978-1983 brain tumour mortality risk higher than expected (5 observed/3.4 expected) but could not be explained by patterns of production work assignments.	Workers potentially exposed to multiple chemicals. No quantitative exposure data and no data on individual chemicals.
Sweeney et al. (1986)[44]	Type of study: Retrospective cohort mortality study. Country: USA. Type of industry: chemical plant. Participants: 2,510 males (90% white, 10% non-white) who worked >1 day at the plant between 1952-77. Control: expected mortality values based on national rates.	No information on exposure levels. Overall and cause-specific standardized mortality ratios (SMRs) and confidence intervals (CI) were calculated. Appropriate statistical analysis was performed. Work histories and smoking status were not taken into account.	Mortality: All causes: lower than expected (observed 156, expected 211). Malignancies or other causes of death: no significant increases.	Workers potentially exposed to multiple chemicals. No quantitative exposure data and no data on individual chemicals. Low power due to small sample size and small observed total number of deaths.
Benson and Teta (1993)[42]	Type of study: Retrospective cohort mortality study. Country: USA. Type of industry: chlorohydrin production at Union Carbide plant Participants: 278 men who were ever assigned to the chlorohydrin production unit between 1940-67. Follow-up period: 1940-88. Control: expected mortality values based on national rates.	No information on exposure levels. Mean duration in chlorohydrin unit / of follow-up: 5.9 / 36.5 years. Overall and cause-specific standardized mortality ratios (SMRs) and confidence intervals (CI) were calculated. Appropriate statistical analysis was performed. Work histories and smoking status were not taken into account.	Mortality: All causes: Observed 147, SMR 104 (CI 88-123). Excess risk for: Pancreatic cancer: Observed 8, SMR 492 (158-1140), p<0.01; Lymphatic and haematopoietic cancers: Observed 8, SMR 294 (127-580), p<0.05.	Workers potentially exposed to multiple chemicals. No quantitative exposure data and no data on individual chemicals.

Reference	Study design and population	Data on exposure and health assessment	Results	Remarks
Olsen et al. (1997)[43]	Type of study: Retrospective cohort mortality study. Country: USA. Type of industry: chlorohydrin production at Dow Chemical plants. Participants: 1,361 men with >1 month workplace experience in 1940-92, in ethylene chlorohydrin and propylene chlorohydrin process areas. Control: expected mortality values based on national rates.	No information on exposure levels. Overall and cause-specific standardized mortality ratios (SMRs) and confidence intervals (CI) were calculated. Appropriate statistical analysis was performed. Smoking status not taken into account.	Mortality: All causes: Observed 300, SMR 89 (CI 79-100). No excess risk for 'all malignant neoplasms' or any specific neoplasm.	Workers potentially exposed to multiple chemicals. No quantitative exposure data and no data on individual chemicals.

Table 3. 1,2-Dichloroethane, case-control studies

References	Study design and population	Data on exposure and health assessment	Results	Remarks
Austin and Schnatter (1983)[47]	Type of study: Case control Country: USA. Type of industry: petrochemical plant. Participants: Cases: 21 primary brain tumour decedents who had worked at the plant, identified through death certificate and tumour registries searches; Control: 2 groups of 80 former employees of the same plant, randomly selected from 450 decedents known to the company; one group was a strictly non-cancer group.	Exposure status based on employment records. An employee was 'exposed' /'unexposed' to a given chemical if he ever / never worked in a department associated with that chemical. Exposure determinations could not be made for 10/21 cases and about 60% of controls. Participants were potentially exposed to other chemicals, including known or suspected carcinogens. Study focused on malignant brain neoplasms. Overall and 15-year latency analyses were performed. The authors note limited testing for statistical significance.	Proportion of cases exposed was comparable with proportion of controls exposed. Proportions exposed: cases (total brain tumours), non-cancer control, 2nd control, resp.: No latency: 45.5, 42.4 and 45.2% At least 15 years latency: 40.0, 32.2 and 34.6%	Workers potentially exposed to multiple chemicals. Small number of cases. No quantitative exposure data. Potential exposure outside the plant not considered. No data on confounders.
Sobel et al. (1986)[49]	Type of study: Case-control. Country: USA. Type of industry: multi-chemical production plant. Participants: 14 soft tissue sarcoma cancer cases identified from death certificates; 9 matched controls per case.	Exposure status based on company work histories. Only one case was potentially exposed to 1,2-dichloroethane. Participants were potentially exposed to 13 chemicals that have been associated with soft-tissue sarcomas in human/animal studies.	No statistically significant odds ratios for any of the chemicals of interest.	Workers potentially exposed to multiple chemicals. Small number of cases. No quantitative exposure data.

References	Study design and population	Data on exposure and health assessment	Results	Remarks
Dosemeci et al. (1999)[48]	Type of study: Population-based case-control. Country: USA. Type of industry: miscellaneous. Participants: 438 renal cell carcinoma cases identified from a state-wide cancer registry; 687 age- and gender- stratified controls obtained with random-digit dialing or from a health care finance listing.	Exposure data from occupational history information obtained by trained interviewers. Exposure status of subjects determined by standard occupational and industrial classification schemes and job exposure matrices for all organic solvents combined, 9 individual chlorinated aliphatic hydrocarbons (CAHCs) and CAHCs combined. Only 9% of cases and 7% of controls were potentially exposed to 1,2-dichloroethane.	Odds ratio for 1,2-dichloroethane not statistically significantly increased. Odds ratio [95% confidence interval]: Men: 1.1 [0.7-1.9]; Women: 2.3 [0.9-5.9]	Workers potentially exposed to multiple chemicals. Small number of cases. Limited occupational history (only current and usual jobs). No quantitative exposure data. Potential survival bias (cases who died were excluded from analysis).
Kernan et al. (1999)[46]	Type of study: Population-based case-control. Country: USA, 24 states Type of industry: miscellaneous. Participants: 63,097 cases who died from pancreatic cancer identified from death certificates; 252,386 matched controls who died from causes other than cancer in same period (1984-93).	Exposure assessment based on occupation and industry on death certificates. Job exposure matrices for all organic solvents combined, 9 individual chlorinated aliphatic hydrocarbons (CAHCs) and CAHCs combined were used to evaluate exposure to solvents (intensity and probability were scored as none, low, medium or high).	Increased risk associated with high probability of exposure to 1,2-dichloroethane for white men and women: Odds ratio [95% confidence interval]: White men (16 exposed cases): 1.6 [0.9-2.8]; White women (8 exposed cases):2.1 [0.9-5.0] There was no increased risk associated with intensity of exposure to 1,2-dichloroethane.	Workers potentially exposed to multiple chemicals. No data on duration of employment, no data on other than most recent occupation. No quantitative exposure data. Possible misdiagnosis of pancreatic cancer. No data on confounders (cigarette smoking socioeconomic status, other lifestyle factors).
Hansen (2000)[45]	Type of study: Case-control, register based. Country: Denmark. Type of industry: companies with specific trade codes (see 2nd column of this table). Participants: male employees selected from national pension fund, 230 breast cancer cases identified from Danish Cancer Registry; 12,880 age-matched controls.	Exposure status based on job type and trade code; blue collar workers who had had >3 months of employment within companies with trade codes of service station, vehicle maintenance, wholesale trade of gasoline or car repair shops were classified as exposed to gasoline vapour and its combustion products. Odds ratios, adjusted for socioeconomic status, were estimated by conditional logistic regression analysis.	Odds ratio [95% confidence interval] for exposure to gasoline and combustion products: No lag time: 2.2 [1.4-3.6]; >10 years lag time 2.5 [1.3-4.5].	Workers potentially exposed to multiple chemicals. Linking of cancer excess to individual chemicals not possible. No quantitative exposure data and no data on individual chemicals.

B animal studies

Table 4. 1,2-Dichloroethane, animal studies

Reference	Study design and animal species	Data on exposure and effect endpoints	Results	Remarks
Nagano et al. (1998); Nagano et al. (2006)[9,10]	F344/DuCrj rats(50/sex/group).	Inhalation exposure Purity: >99% Exposure: 0, 10, 40, 160 ppm (0, 40, 160, 640 mg/m^3) (6h.d, 5d.wk) Xpo= 104 weeks Xpe= 104 weeks Statistical analysis: Peto's test (trend), and Fisher's exact test.	Survival: After 104 weeks for 0, 40, 160, and 640 mg/m^3 group, resp.: 74, 70, 64, 74% (males), 70, 82, 74, 76% (females), resp. Adverse effects: subcutaneous masses in breast, back, abdominal and perigenital areas, no exposure-related chances in haematological, blood chemical or urinary parameters Tumours: 0, 40, 160, 640 mg/m^3 groups, resp.: *Subcutis fibroma*: male: 6/50, 9/50 12/50, 15/50; female: 0/50, 0/50, 1/50, 5/50 ($p<0.05$) *Mammary gland adenoma*: male: 1/50, 2/50, 0/50, 2/50; female: 3/50, 5/50, 5/50, 11/50 ($p<0.05$). *Mammary gland fibroadenoma*: male: 0/50, 0/50, 1/50, 5/50 ($p<0.05$); female: 4/50, 1/50, 6/50, 13/50 ($p<0.05$). *Peritoneum mesothelioma*: male:1/50, 1/50, 1/50, 5/50. *Mammary gland adenocarcinoma*: female: 1/50, 2/50, 0/50, 5/50.	Klimisch score: 2 Well-performed study, adequate for carcinogenicity assessment *Deficiencies*: -
Nagano et al. (1998); Nagano et al. (2006)[9,10]	Crj:BDF1 mice (50 sex/group).	Inhalation exposure Purity: >99% Exposure: 0, 10, 30, 90 ppm (0, 40, 120, 360 mg/m^3) (6 h/d, 5 d/wk) Xpo= 104 weeks Xpe= 104 weeks Statistical analysis: Peto's test (trend), and Fisher's exact test.	Survival: After 104 weeks for 0, 40, 120, and 360 mg/m^3 group, resp.: 78, 65, 70, 74% (males), 69, 56, 38 ($p<0.01$), 52% (females) males and females, resp. Adverse effects: subcutaneous masses in breast, back, and abdominal area in females, no exposure-related chances in haematological, blood chemical or urinary parameters Tumours: 0, 40, 120, 360 mg/m^3 resp.: Only male: *Liver hemangiosarcoma*: 0/50, 4/49, 6/50 ($p<0.05$), 5/50 ($p<0.05$) Only female. *Lung bronchio-alveolar adenoma*: 4/49, 1/50, 3/50, 8/50, *carcinoma*: 1/49, 0/50, 1/50, 3/50. *Uterus endometrial stromal polyp*: 2/49, 0/50, 1/50, 6/50. *Mammary gland adenocarcinoma*: 1/49, 2/50, 1/50, 6/50. *Liver hepatocellular adenoma*: 1/49, 1/50, 1/50, 6/50, *carcinoma*: 1/49, 0/50, 1/50, 0/50. *Lymph node malignant lymphoma*: 6/49, 17/50 ($p<0.05$), 22/50 ($p<0.01$), 12/50.	Klimisch score: 2 Well-performed study, adequate for carcinogenicity assessment *Deficiencies*: -

Reference	Study design and animal species	Data on exposure and effect endpoints	Results	Remarks
NCI (1978); Ward (1980); Weisburger (1977)[14-16]	Osborne-Mendal rats. Control: 20 animals/sex/group (untreated and vehicle treated) Exposed: 50 animals/sex/ group.	Oral gavage Solvent: corn oil TWA exposure doses (mg/kg bw/ day): 0, 47, 95 (5 d/wk) Xpo=78 weeks Xpe= 110 weeks Statistical analysis: one –tailed Fischer exact test.	Survival: Survival markedly decreased at high-dose in both sexes (only 50% survival after about one year). Adverse effects: hunched appearance and transient laboured respiration, abdominal urine stains, cloudy or squinted eyes, and eyes with a reddish crust appeared more in the exposed groups in the first year, incidence of palpable nodules and/or tissue masses slightly greater in treated compared to controls. Tumours (*= sign. compared to pooled vehicle group, **= sign. compared to matched vehicle group): pooled vehicle, matched vehicle, low dose, high dose, resp.: *Hemangiosarcoma circulatory system*: Male: 1/60, 0/20, 9/50 (p=0.003*, p=0.039**), 7/50 (p=0.016*); Female: 0/59, 0/20, 4/50 (p=0.041*), 4/50 (p=0.041*). *Pituitary chromophobe adenoma*: Male: 3/60, 2/20, 1/50, 4/49; Female: 13/59, 7/20, 7/50, 5/49 (p=0.020**). *Subcutanous fibroma*: Male : 0/60, 0/20, 5/50 (p=0.017*), 6/50 (p=0.007*). *Tunica vaginalis mesothelioma*: Male : 0/60, 0/20, 3/50, 0/50. *Stomach squamous-cell carcinoma*: Male: 0/60, 0/20, 3/50, 9/50 (p=0.001*, p=0.039**). *Thyroid follicular-cell adenoma*: Female: 0/58, 0/20, 3/50, 0/50. *Mammary gland adenocarcinoma NOS*: Female: 1/59, 0/20, 1/50, 18/50 (p<0.001*, p=0.002**). *Mammary gland fibroadenoma*: Female: 5/59, 0/20, 14/50 (p=0.007*, p=0.005**), 8/50.	Klimisch score: 2. Well performed study, adequate for carcinogenicity assessment *Deficiencies*: doses changed during the study, high mortality in high dose groups early in study, exposure less than life-span.
NCI (1978); Ward (1980); Weisburger (1977)[14-16]	B6C3F1 mice 50 animals/sex/ exposed group 20 animals/sex/ control group.	Oral gavage Solvent: corn oil TWA exposure doses (mg/kg bw/ day): 0, 97, 195 male, 0, 149, 299 female (5 d/wk) Xpo= 78 weeks Xpe= 91 weeks Statistical analysis: one –tailed Fischer exact test	Survival: Survival markedly decreased at high-dose in females, possibly tumour-related (72% died between week 60-80). Survival of high-dose males and vehicle control males was good whereas low-dose males and untreated control males had poor survival. Adverse effects: mean body weight depression for high dose females, incidence of palpable nodules and/or tissue masses and swelling abdominal midline slightly greater in treated compared to controls. Tumours: pooled vehicle, matched vehicle, low dose, high dose (*= sign. compared to pooled vehicle group, **= sign. compared to matched vehicle group). *Alveolar/bronchiolar adenoma*: Male: 0/59, 0/19, 1/47, 15/48 (p<0.001*, p=0.003**); Female: 2/60, 1/20, 7/50 (p=0.046*), 15/48 (p<0.001*, p=0.016**). *Hematopoetic system malignant lymphoma*: Male: 4/59, 2/19, 8/47, 5/48; Female: 8/60, 4/20, 10/50, 2/48. *Stomach squamous-cell carcinoma*: Male: 1/59, 1/19, 1/46, 2/46;Female: 1/60, 1/20, 2/50, 5/48. *Subcutanous fibrosarcoma*: Male:1/59, 0/19, 0/47, 4/48. *Hepatocellular carcinoma liver*: Male: 4/59, 1/19, 6/47, 12/48 (p=0.009*). *Mammary gland adenocarcinoma NOS*: Female: 0/60, 0/20, 9/50 (p=0.001*, p=0.039**), 7/48 (p=0.003*). *Endometrium/uterus adenocarcinoma NOS*: Female: 1/60, 0/20, 3/49, 4/47. *Uterus endometrial stromal polyp*: Female: 0/60, 0/20, 3/49, 2/47. *Uterus endometrial stromal sarcoma*: Female: 0/60, 0/20, 2/49, 3/47.	Klimisch score: 2 Well-performed study, adequate for carcinogenicity assessment. *Deficiencies*: doses changed during the study, high mortality early in study in high dose females, exposure less than life-span.

Reference	Study design and animal species	Data on exposure and effect endpoints	Results	Remarks
Maltoni et al. (1980, 1982)[12,52]	Sprague-Dawley rats 90 animals/sex/ group Controls: one group in an exposure chamber, one group in nearby room during exposure of the treated animals.	Inhalation exposure. Purity: 99.8%. Exposure: 0, 5, 10, 50, 250 ppm (0, 20, 40, 200, 1,000 mg/m^3) (reduced to 600 mg/m^3 after few weeks) (7 h/d, 5 d/wk) Xpo= 78 weeks Xpe= lifespan Statistical analysis: Chi-Square analysis.	Survival: at 104 weeks: Male:12/90, 16/90, 45/90, 13/90, 17/90,10/90, Female: 22/90, 36/90, 48/90, 26/90, 29/90, 21/90 for control chamber, control nearby room, 20, 40, 200, 600-1,000 mg/m^3, resp. Adverse effects: high toxicity after a few weeks of 1,000 mg/m^3. Tumours: *Mammary tumours (*fibromas and fibroadenoma*)*: Male: 7/90, 3/90, 11/90, 3/89, 7/90, 7/89; Female: 27/90, 47/90 (p<0.01), 56/90 (p<0.001), 33/90, 49/90 (p<0.01), 47/90 (p<0.01) for controls exposure chamber, controls nearby room, 20, 40, 200, and 600-1,000 mg/m^3, resp.; p-values from comparisons with controls in exposure chamber. Incidences of other tumours similar to the control groups.	Klimisch score: 2 Well-performed study, adequate for carcinogenicity assessment. *Deficiencies*: exposure less than life-span, no information on non-cancer effects, MTD exceeded.
Maltoni et al. (1980)[12]	Swiss mice Controls: 115 and 134, male and female, resp. Exposed: 90 animals/sex/ group.	Inhalation exposure Purity: 99.8%. Exposure: 0, 5, 10, 50, 250 ppm (0, 20, 40, 200, 1,000 mg/m^3) (reduced to 600 mg/m^3 after few weeks) (7 h/d, 5 d/wk) Xpo= 78 weeks Xpe= lifespan Statistical analysis: Chi-Square analysis.	Survival: at 78 weeks for 0, 20, 40, 200, 600-1000 mg/m^3 male and female, resp.: 42/115, 26/90, 34/90, 30/90, 26/90 (males); 76/134, 68/90, 50/90, 49/90, 44/90 (females). Adverse effects: high toxicity after a few weeks of 1,000 mg/m^3. Tumours: tumour incidences similar between groups.	Klimisch score: 2. Well–performed study, adequate for carcinogenicity assessment. *Deficiencies*: exposure less than life-span, no information on non-cancer effects, MTD exceeded, housing condition on exposure days not identical between exposed and control mice.
Cheever et al. (1990)[11]	Sprague-Dawley rats. 50 animals/sex/ group.	Inhalation exposure Purity: >99% Exposure: 0, 50 ppm (0, 200 mg/m^3) (7h/d, 5d/wk) Xpo= 2 years Xpe= 2 years Statistical analysis: Fisher's exact test.	Survival: After 2-years: 58, 60% (males); 54, 64% (females), control and exposed rats, resp. Adverse effects: no adverse effects were observed, except increased testicular lesions 10 and 24%, for control and exposed rats, resp. Tumours: all tumour incidences similar between groups.	Klimisch score: 2. Well performed study, adequate for carcinogenicity assessment. *Deficiencies*: only one concentration tested, which was well below the MTD.

Reference	Study design and animal species	Data on exposure and effect endpoints	Results	Remarks
Van Duuren et al. (1979)[53]	Ha:ICR Swiss female mice. 30 animals/group.	Dermal application Exposure: 0, 42, 126 mg (3 d/wk) Solvent: 0.2 mL acetone Xpo= somewhere between 440-595 days Xpe= not specified Statistical analysis: Chi-square analysis.	Survival: not specified, median survival range 317 to more than 589 days. Tumours: 0 (0.1ml acetone), 42, 126 mg, resp.: *Lung papilloma*: 11/30, 17/30, 26/30 ($p<0.0005$). *Stomach papilloma and squamous-cell carcinoma*: 2/30, 1/30, 3/30.	Klimisch score: 3. Supportive study. *Deficiencies*: insufficient number of animals used, only tested in one sex, mice were not restrained from licking, no information on non-cancer effects, exposure and observation period were not specified, no appropriate negative control used.
Suguro et al. (2017)[54]	CB6FI-Tg rasH2 mice. 10 animals/sex/ group.	Dermal application Exposure: 0, 126 mg (3 d/wk) Solvent: 0.2 mL acetone Xpo= 26 weeks Xpe= 26 weeks Statistical analysis: Fisher's exact probability test or Aspin-Welch's test.	Survival: 5 treated female mice were euthanized in a moribund condition at 7-25 weeks. One control female was euthanized in week 26, due to hemangiosarcoma of the uterus. Bronchiolo-alveolar hyperplastic and neoplastic lesions: Hyperplasia: 0/10 and 1/10 (males); 0/10 and 6/10** (females). Adenoma: 0/10 and 8/10** (males); 0/10 and 7/10** (females). Adenocarcinoma: 0/10 and 5/10* (males); 0/10 and 10/10** (females) (*$p<0.05$, **$p<0.01$).	Klimisch score: 2. Well performed study, not adequate for carcinogenicity assessment. *Deficiencies*: Sensitive transgenic animal model, route not appropriate, only one dose tested.
Theiss et al. (1977)[55]	Strain A/St male mice. Control: 50 animals. Exposed: 20 animals/ group.	Intra-peritoneal injections. Solvent: Tricaprylin. Exposure: 0, 20, 40, 100 mg/kg/ injection (3x/wk) Xpo= 8 weeks Xpe= 24 weeks Statistical analysis: student t-test.	Survival: 46/50, 14/20, 16/20, 20/20. Tumours: average number per mouse: 0, 80, 200, 400 resp.: *Lung adenoma*: 0.39, 0.21, 0.44, 0.75.	Klimisch score: 3. Supportive study. *Deficiencies*: no individual animal data, exposure and observation period too short, only one benign tumour investigated, only one sex used, no information on non-cancer effects.

X_{po} = duration of exposure; X_{pe} = duration of the experiment; sign. = significant; TWA = time-weighted average; MTD = maximal tolerated dose; Klimisch scores were based on Klimisch et al.[59]

C BMD-analysis

Software	Proast, version 65.7
BMR, risk type	10%, extra risk
BMDL	Lowest 95% confidence interval of the BMD
Model fit and averaging	The fit of a model is measured by the comparison with the best fitting model (the one with the lowest AIC (AICmin)). If [AICmodel < AICmin + 2] then both models are similar and the tested model provides a fit comparable with the best fitting model. The weight of a model depends on the fit – models with lower fit are attributed lower weights for model averaging.
Data source	Nagano K, Umeda Y, Senoh H, et al. Carcinogenicity and chronic toxicity in rats and mice exposed by inhalation to 1,2-dichloroethane for two years. Journal of Occupational Health. 2006;48(6):424-436.[10]
Exposure design	Crj:BDF1 mice exposed via inhalation for 104 weeks (6 hours/day, 5 days/week); experimental period 104 weeks
Effect parameter	Incidence of mammary gland adenocarcinoma in female mice

Table 5. Data on exposure and response

Dose (mg/m³)	Number of female mice per dose	Number of female mice with mammary gland adenocarcinoma
0	49	1
40	50	2
120	50	1
360	50	6

Table 6. Outcome of BMD-analysis for female mice

Model	No. Par.	Log-lik.	AIC	BMDL	BMDU	BMD	Conv.	Weight
Null	1	-39.65	81.3	NA	NA	NA	NA	
Full	4	-36.53	81.06	NA	NA	NA	NA	
two stage	3	-36.92	79.84	260	736	374	Yes	0.0763
log.logist	3	-36.76	79.52	235	2,920	361	Yes	0.0895
Weibull	3	-36.76	79.52	235	3,040	361	Yes	0.0895
Log.prob	3	-36.76	79.52	234	3,720	362	Yes	0.0895
gamma	3	-36.76	79.52	236	2,870	362	Yes	0.0895
logistic	2	-36.97	77.94	269	917	367	Yes	0.1972
probit	2	-37	78	259	1,040	371	Yes	0.1914
LVM: Expon. M3-	3	-36.77	79.54	238	2,330	362	Yes	0.0886
LVM: Expon. M3-	3	-36.77	79.54	236	2,520	363	yes	0.0886

Final BMDL	Final BMDU	Final BMD[#]
267	840	366

[#] If [AICmodel > AICnull - 2] than there is no trend in the data. Due to the limited data, the final BMD is not calculated based on geometric mean but using the separate BMDs and subsequent weights.

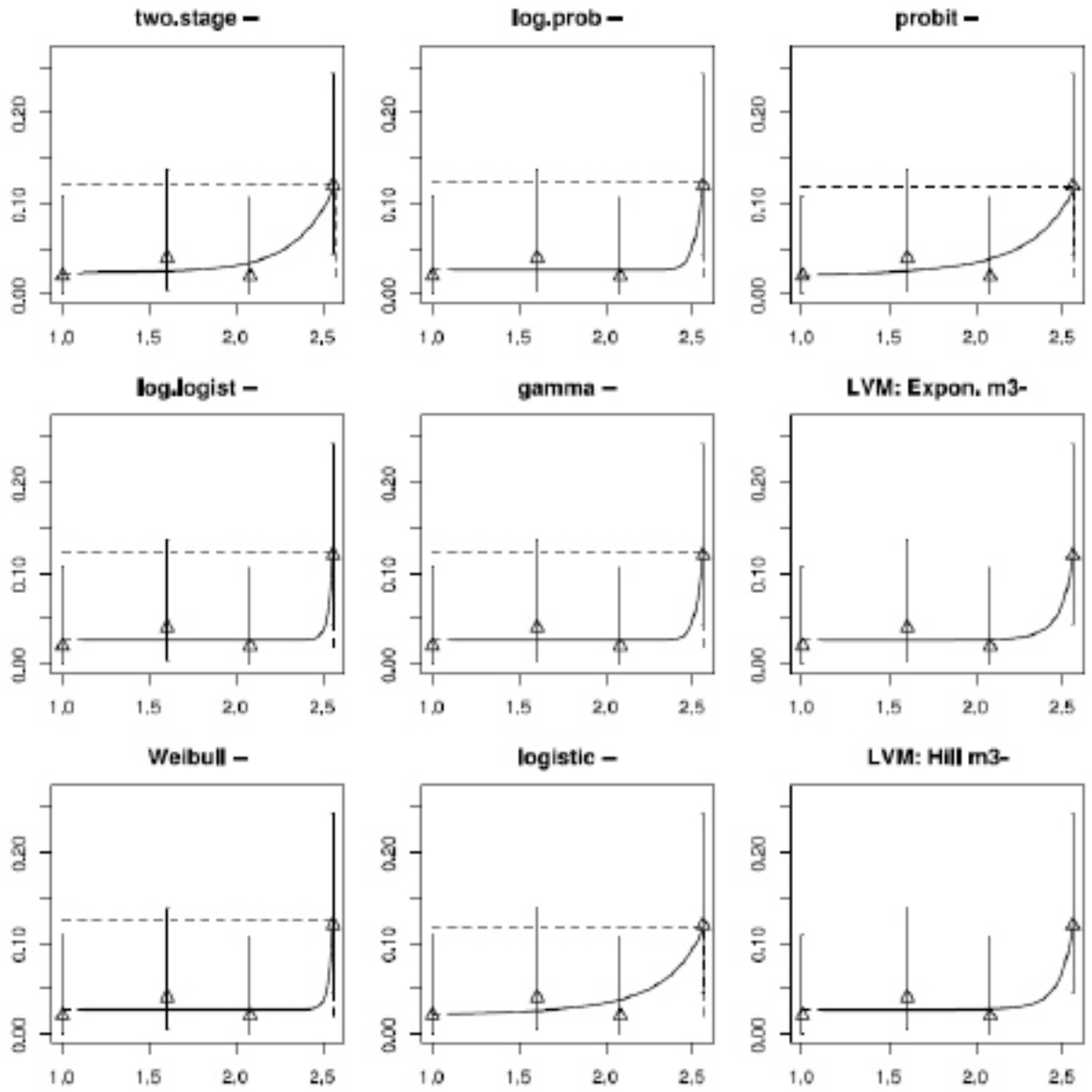

Figure 1. BMD Plots

D recommendation of the Subcommittee on Classification of carcinogenic substances

D.1 Scope

For carcinogens, the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council derives either a health-based recommended occupational exposure limit (HBR OEL) or a health-based calculated occupational cancer risk value (HBC-OCRV), dependent on their mechanism of action. For non-genotoxic carcinogens and non-stochastic genotoxic carcinogens, it is assumed that the carcinogenic effects only occur when exposure levels exceed a certain threshold. For such substances, the Committee derives a HBR OEL. For stochastic genotoxic carcinogens, and genotoxic carcinogens for which the mechanism of action is unknown but for which a stochastic mechanism is not unlikely, it is assumed that any level of exposure is associated with a certain risk for developing cancer. For these substances, a HBC-OCRV is derived.

In order to establish the appropriate approach, the Subcommittee on the Classification of carcinogenic substances was requested by DECOS to evaluate the carcinogenic properties of 1,2-dichloroethane and in

particular, its genotoxic mode of action. The members of the Subcommittee are listed at the end of this Annex.

This Annex contains the conclusions of the Subcommittee. A summary of the carcinogenicity and genotoxicity data is provided in separate sections of the report.

D.2 Conclusion on the carcinogenicity of 1,2-dichloroethane

The Subcommittee concludes that in all epidemiological studies workers/residents were likely co-exposed to numerous known or suspected human carcinogens, therefore, the human data is inadequate to evaluate the relationship between human cancer and exposure to 1,2-dichloroethane.

Animal studies have shown 1,2-dichloroethane can cause mammary gland fibroadenoma, subcutis fibroma, peritoneum mesothelioma, and hemangiosarcomas in male rats, and subcutis fibroma, mammary gland adenoma/adeno-carcinoma, fibroadenoma and subcutis fibroma in female rats. 1,2-Dichloroethane also causes bronchio-alveolar adenomas and carcinomas in the lung, endometrial stromal polyps in the uterus, adeno-carcinoma in the mammary gland, and hepatocellular adenomas in female mice and alveolar/bronchiolar adenomas in both female and male mice. Based on these findings, the Subcommittee concludes that there is sufficient evidence for carcinogenicity of 1,2-dichloroethane in animals. The Subcommittee notes that the carcinogenicity data do not describe a full dose-response relationship.

D.3 Conclusions on the genotoxicity of 1,2-dichloroethane

1,2-Dichloroethane is genotoxic in vitro by inducing gene mutations and chromosomal aberrations. The substance can also form DNA-adducts in the presence of a metabolic activation system. In vivo,1,2-dichloroethane has been shown to induce DNA damage, including the formation of DNA adducts. Four out of 5 micronucleus tests were negative, and a mouse LacZ gene mutation assay in liver and testis revealed no induction of mutants.

The Subcommittee notes that 1,2-dichloroethane is a clear in vitro mutagen. In vivo, 1,2-dichloroethane binds to DNA and causes DNA damage. Genotoxicity data are available that indicate that 1,2-dichloroethane does not induce chromosomal aberrations in mice. However, positive results have been reported in a micronucleus/chromosomal aberration test in rats. The Subcommittee notes that this study showed no apparent dose-response, and negative control values were unusually low. Further, this study has questionable reporting. No increased mutant frequency was observed in a LacZ gene mutation assay in mice. However, this in vivo gene mutation assay has not been conducted according to general guidelines (for instance, a positive control is lacking). Overall, the in vivo genotoxicity data are limited and no definitive conclusions can be drawn from

these data. The Committee concludes, based on the results of the positive genotoxicity assays in vitro and indicator tests in vivo and the absence of conclusive in vivo genotoxicity data, that 1,2-dichloroethane is a low potency mutagen and a stochastic genotoxic carcinogen.

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- E. De Rijk, Toxicologic Pathologist, Charles River Laboratories, ‘s Hertogenbosch
- J.J. Vlaanderen, Epidemiologist, Institute for Risk Assessment Sciences, Utrecht
- J. van Benthem, Genetic toxicologist, RIVM, Bilthoven, *structurally consulted expert*

Scientific secretary:

- S.R. Vink, The Health Council of the Netherlands, The Hague

Meeting dates:

- March 20 and April 26, 2019

Committee and consuted experts

Members of the Dutch Expert Committee on Occupational Safety (DECOS) for the advisory report 1,2-dichloroethane:

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